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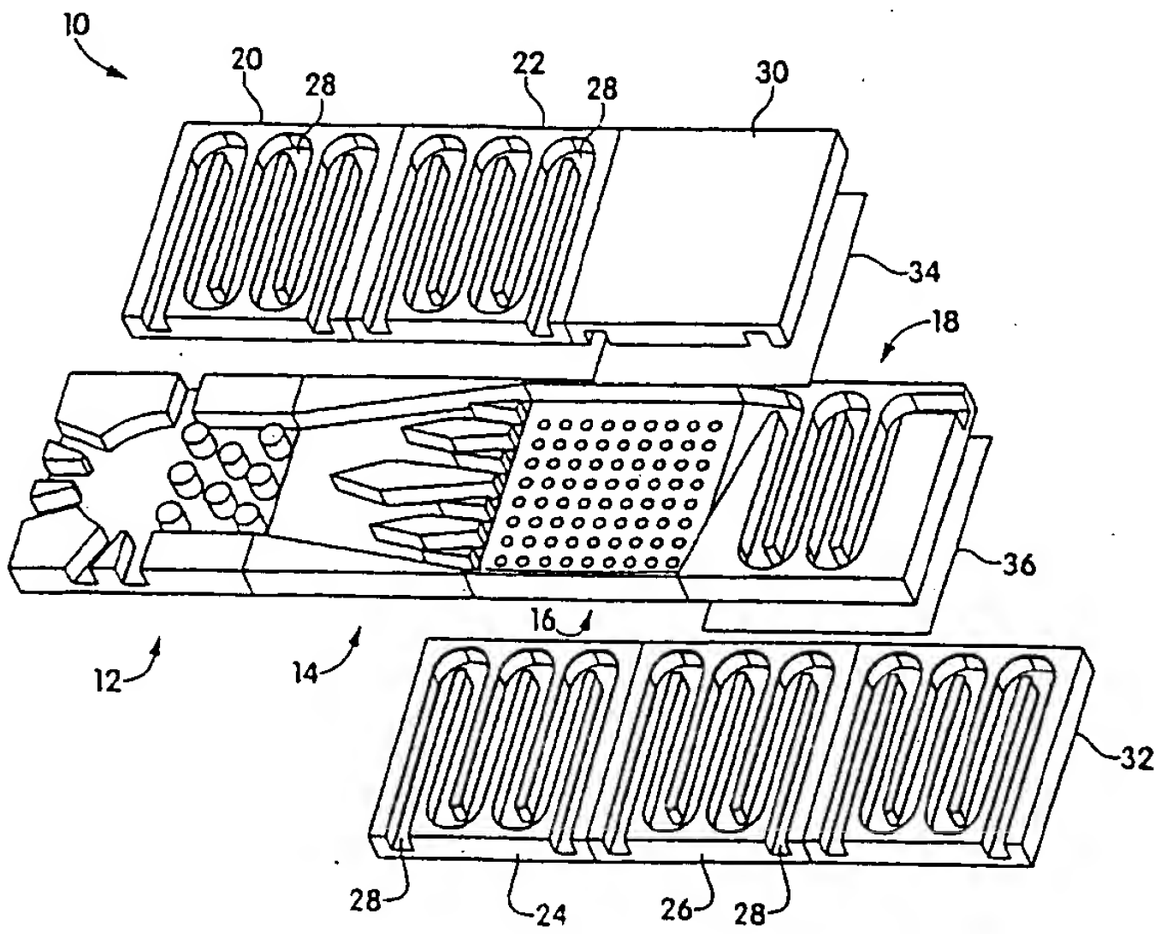

(57) Abstract: Chemical and biological reactors, including microreactors, are provided. Exemplary reactors include a plurality of reactors operable in parallel, where each reactor has a small volume, and together, the reactors produce a large volume of product. Reaction systems can include mixing chambers (12), heating/dispersion units (14), reaction chambers (16), and separation units (18). Components of the reactors can be readily formed from a variety of materials. For example, they can be etched from silicon. Components are connectable to and separable from each other to form a variety of types of reactors, and the reactors can be attachable to and separable from each other to add significant flexibility in parallel and/or series reactor operations.

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MICROREACTOR

Field of the Invention

The present invention relates generally to chemical or biochemical microreactors, and more particularly to a microreactor for the production of the product of a chemical or biochemical reaction, including a plurality of individuated microreactors constructed to operate in parallel.

Background of the Invention

A wide variety of reaction systems are known for the production of the product of chemical or biochemical reactions. Chemical plants involving catalysis, biochemical fermenters, pharmaceutical production plants, and a host of other systems are well-known.

Systems for housing chemical and biochemical reactions not necessarily for the production of product also are known. For example, continuous-flow systems for the detection of various analytes in bodily fluids including blood, such as oxygen, glucose, and the like are well known.

In many of these and other systems, the capacity of the system (the volume of material that the system is designed to produce, process, or analyze) is adjusted in accordance with the volume of reactant, product, or analyte desirably processed or analyzed. For example, in large-scale chemical or pharmaceutical production, reactors are generally made as large as possible to generate as large a volume of product as possible. Conversely, in many areas of clinical diagnosis, where it is desirable to obtain as much information as possible from as small a physiological sample as possible (e.g., from a tiny drop of blood), it is a goal to minimize the size of reaction chambers of sensors. Several examples of small-scale reactor systems, including those used in clinical diagnoses and other applications, follow.

U.S. patent no. 5,387,329 (Foos, et al.; February 7, 1995) describes an extended use planar clinical sensor for sensing oxygen levels in a blood sample.

U.S. patent no. 5,985,119 (Zanzucchi, et al.; November 16, 1999) describes small reaction cells for performing synthetic processes in a liquid distribution system. A variety of chemical reactions including catabolic, anabolic reactions, oxidation, reduction, DNA synthesis, etc. are described.

U.S. patent no. 5,674,742 (Northrup, et al.; October 7, 1997) describes an integrated microfabricated instrument for manipulation, reaction, and detection of microliter to picoliter samples. The system purportedly is suitable for biochemical reactions, particularly DNA-based reactions such as the polymerase chain reaction.

U.S. patent no. 5,993,750 (Ghosh, et al.; November 30, 1999) describes an integrated micro-ceramic chemical plant having a unitary ceramic body formed from multiple ceramic layers in the green state which are sintered together defining a mixing chamber, passages for delivering and reacting fluids, and means for delivering mixed chemicals to exit from the device.

Biochemical processing typically involves the use of a live microorganism (cells) to produce a substance of interest. Biochemical and biomedical processing account for about 50% of the total drug, protein and raw amino-acid production worldwide. Approximately 90% of the research and development (R&D) budget in pharmaceutical industries is currently spent in biotechnology areas.

Currently bioreactors (fermentors) have several significant operational limitations. The most important being maximum reactor size which is linked to aeration properties, to nutrient distribution, and to heat transfer properties. During the progression of fermentation, the growth rate for cells accelerates, and the measures required to supply the necessary nutrients and oxygen sets physical and mechanical constraints on the vessel within which the cells are contained. Powerful and costly drives are needed to compensate for inefficient mixing and low mass-transfer rates. Additionally, as metabolism of cells accelerates, the cells generate increased heat which needs to be dissipated from the broth.

The heat transfer characteristics of the broth and the vessel (including heat exchanger) impose serious constraints on the reaction scale possible (see Table 1). While the particular heat load and power requirements are specific to the reaction, the scale of reaction generally approaches limitations at ~10m^3 as in the case of *E. coli* fermentation (Table 1). The amount of heat to be dissipated becomes excessive due to limits on heat transfer coefficients of the broth and vessel. Consequently, the system of vessel and broth will rise in temperature. Unfortunately, biological compounds often have a relatively low upper limit on temperature for which to survive (< 45 °C for many). Additionally, power consumption to disperse nutrients and oxygen and coolant

requirements to control temperature make the process economically unfeasible (see Table 1).

Table 1: Oxygen- and Heat- Transfer Requirements for *E. coli*: Effects of Scale

OTR (mmol/L· h)	Volume[a] (m^3)	Pressure (psig)	Power (hp)	Heat Load (Btu/h)	Coolant[b] (°F)
150	1	15	5.0	84 000	40
200	1	25	4.9	107 000	40
300	1	35	7.1	161 000	40
400	1	35	6.9	208 000	40
150	10	15	50.2	884 000	40
200	10	25	50.0	1 078 000	40
300	10	35	75.7	1 621 000	22
400	10	35	77.0	2 096 000	5

[a] Liquid volume

[b] Coolant flow is 35 gal/min for 1-m^3 vessel and 100 gal/min for 10-m^3 vessel

[c] Charles, M. and Wilson, J. Fermentor Design; In: *Bioprocess Engineering*; Lydersen, B. K., D'Elia, N. A., Nelson, K.L., Ed.; John Wiley & Sons, Inc., New York, 1994.

Aside from reactor scalability, the design of conventional fermentors has other drawbacks. Due to the batch and semi-batch nature of the process, product throughput is low. Also, the complexity and coupled nature of the reaction parameters, as well as the requirement of narrow ranges for these parameters, makes control of the system difficult. Internal to the system, heterogeneity in nutrient and oxygen distribution due to mixing dynamics creates pockets in the broth characterized by insufficient nutrients or oxygen resulting in cell death. Finally, agitation used to produce as homogeneous a solution as possible (typically involving impellar string to simultaneously mix both cells and feeds of oxygen and nutrients) causes high strains which can fracture cell membranes and cause denaturation.

While a wide variety of useful reactors for a variety of chemical and biological reactions, on a variety of size scales exist, a need exists in the art for improved reactors. In particular, there is a current need to significantly improve the design of bioreactors especially as the pharmaceutical and biomedical industries shift increasingly towards bioprocessing.

Summary of the Invention

The present invention provides systems, methods, and reactors associated with small-scale chemical or biochemical reactions.

In one aspect the invention provides a chemical or biochemical reactor. The reactor includes a reaction unit including a chamber having a volume of less than one milliliter. The chamber includes an inlet connectable to a source of a chemical or biological starting material and an outlet for release of a product of a chemical or biological reaction involving the starting material. A collection chamber is connectable to the outlet of the reaction chamber. The collection chamber has a volume of greater than one liter.

In another aspect the invention involves a chemical or biochemical reactor system. The system includes a mixing chamber including a plurality of inlets connectable to a plurality of sources of chemical or biochemical reagents, and an outlet. A reaction chamber is connectable to and removable from the mixing chamber, and has a volume of less than one milliliter. The reaction chamber includes an inlet connectable to and removable from the outlet of the mixing chamber, and an outlet for release of a product of a chemical or biological reaction involving the starting material.

In another aspect the invention provides methods. One method includes carrying out a chemical or biological reaction in a plurality of reaction chambers operable in parallel, where each reaction chamber has a volume of less than one milliliter. Product of the reaction is discharged from the plurality of reaction chambers simultaneously into a collection chamber having a volume of greater than one liter.

Other advantages, novel features, and objects of the invention will become apparent from the following detailed description of the invention when considered in conjunction with the accompanying drawings, which are schematic and which are not intended to be drawn to scale. In the figures, each identical or nearly identical component that is illustrated in various figures is represented by a single numeral. For purposes of clarity, not every component is labeled in every figure, nor is every component of each embodiment of the invention shown where illustration is not necessary to allow those of ordinary skill in the art to understand the invention.

Brief Description of the Drawings

Fig. 1 illustrates a microbioreactor of the invention including mixing, heating/dispersion, reaction, and separation units, in expanded view;

Fig. 2 illustrates the system of Fig. 1 as assembled;

Fig. 3 illustrates the mixing unit of the system of Fig. 1;

Fig. 4 is an expanded view of the heating/dispersion unit of the system of Fig. 1;

Fig. 5 is an expanded view of the reaction chamber of the system of Fig. 1; and

Fig. 6 is an expanded view of the separation unit of the system of Fig. 1.

Detailed Description of the Invention

The present invention provides a chemical or biochemical reactor that can be used for a variety of very small-scale techniques. In one embodiment, a microreactor of the invention comprises a matrix of a few millimeters to a few centimeters in size containing reaction channels with dimensions on the order of hundreds of microns. Reagents of interest are allowed to flow through these microchannels, mixed, and reacted together. The products can be recovered, separated, and treated within the system. While one microreactor may be able only to hold and react a few microliters of the substances of interest, the technology allows for easy scalability and tremendous parallelization. With enhanced oxygen and nutrient distribution, a microreactor of the invention demonstrates increased performance in terms of cell viability. The microreactor geometry resembles closely the natural environment of cells whereby diffusional oxygen and nutrient transfer take place through a high surface area, thin layer interface.

With regard to throughput, an array of many microreactors can be built in parallel to generate capacity on a level exceeding that allowed by current vessels and more uniform in product quality than can be obtained in a batch method. Additionally, an advantage is obtained by maintaining production capacity at the scale of reactions typically performed in the laboratory. In general, the coupled parameters for heat and mass transfer that are determined on the lab-scale for a process do not scale linearly with volume. With conventional reactors, as the magnitude of volume is increased 1,000-1,000,000 times for production, these parameters need to be re-evaluated, often involving a large capital-investment. The use of small production volumes, although scaled in parallel, reduces the cost of current scale-up schemes.

Furthermore, the process can be implemented on a simple platform, such as an etched article for example, a silicon wafer. With the effort of semiconductor manufacturing being towards the reduction in the dimensions of channels, an opportunity

to utilize excess capacity within these production facilities (with unused equipment for the larger dimensions) is provided. Mass production of these units can be carried out at very low cost and an array of many reactors, for example thousands of microreactors typically can be built for a price lower than one traditional bioreactor.

Referring now to Fig. 1, a chemical or biochemical reactor in accordance with one embodiment of the invention is illustrated schematically. The reactor of Fig. 1 is, specifically, a microbioreactor for cell cultivation. It is to be understood that this is shown by way of example only, and the invention is not to be limited to this embodiment. For example, systems of the invention can be adapted for pharmaceutical production, hazardous chemical production, or chemical remediation of warfare reagents, etc.

Microreactor 10 includes four general units. A mixing unit 12, a heating/dispersion unit 14, a reaction unit 16, and a separation unit 18. That is, in the embodiment illustrated, processes of mixing, heating, reaction, purification are implemented in series. Although not shown, pressure, temperature, pH, and oxygen sensors can be included, for example embedded within the network to monitor and provide control for the system. Due to the series format, the opportunity for several reaction units in series for multi-step chemical syntheses, for several levels of increased purification, or for micro-analysis units is provided as well.

Fig. 1 shows microreactor 10 in expanded view. As illustrated, each of units 14 and 16 (heating/dispersion and reaction units, respectively) includes at least one adjacent temperature control element 20-26 including a channel 28 through which a temperature-control fluid can be made to flow. As illustrated, temperature control units 20 and 24 are positioned above and below unit 14 and units 22 and 26 are positioned above and below unit 16. Separation unit 18 includes upper and lower extraction solvent fluid units 30 and 32, respectively, separated from unit 18 by membranes 34 and 36, respectively.

Referring now to Fig. 2, reactor 10 is illustrated as assembled. The individual units of microreactor 10 will now be described in greater detail.

Referring now to Fig. 3, mixing unit 12 is illustrated. Mixing unit 12 is designed to provide a homogeneous mixture of starting materials or reactants to be provided to the reaction units, optionally via the heating/dispersion unit. In the specific example of the microbioreactor, mixing unit 12 is designed to provide a homogeneous broth with sufficient nutrients and oxygen, and at the required pH, for cells. Rather than combine

the mixing process with simultaneous nourishment of the cells, the process is performed in a preliminary stage and then fed to the reaction stage where cells are immobilized. In this manner, the cells do not experience any shear stress due to mixing and a homogeneous mixture of feed requirements is guaranteed.

As is the case for other components of the reactor, mixing unit 12 can be manufactured using any convenient process. In preferred embodiments the unit is etched into a substrate such as silicon via known processes such as lithography. Other materials from which mixing unit 12, or other components of the systems of the invention can be fabricated, include glass, fused silica, quartz, ceramics, or suitable plastics. Silicon is preferred. The mixing unit includes a plurality of inlets 40-50 which can receive any of a variety of reactants and/or fluid carriers. Although six inlets are illustrated, essentially any number of inlets from one to tens of hundreds of inlets can be provided. Typically, less than ten inlets are needed for a given reaction. Mixing unit 12 includes an outlet 52 and, between the plurality of inlets and the outlet, a mixing chamber 54 constructed and arranged to coalesce a plurality of reactant fluids provided through the inlets. It is a feature of the embodiment illustrated that the mixing chamber is free of active mixing elements. Instead, the mixing chamber is constructed to cause turbulence in the fluids provided through the inlets thereby mixing and delivering a mixture of the fluids through the outlet without active mixing. Specifically, the mixing unit includes a plurality of obstructions 56 in the flow path that causes mixture of fluid flowing through the flow path. These obstructions can be of essentially any geometrical arrangement. As illustrated, they define small pillars about which the fluid must turbulently flow as it passes from the inlets through the mixing chamber toward the outlet. As used herein "active mixing elements" is meant to define mixing elements such as blades, stirrers, or the like which are movable relative to the reaction chamber itself, that is, movable relative to the walls defining the reaction chamber.

The volume of the mixing chamber, that is, the volume of the interior of mixing unit 12 between the inlets and the outlet, can be very small in preferred embodiments. Specifically, the mixing chamber generally has a volume of less than one liter, preferably less than about 100 microliters, and in some embodiments less than about 10 microliters. The chamber can have a volume of less than about five microliters, or even less than about one microliter.

Specifically, in the microbioreactor illustrated, six separate feed streams empty into the mixing chamber under pressure. One feed stream provides gaseous oxygen (O_2) as a cell requirement. One stream, respectively, provides carbon dioxide (CO_2) and nitrogen (N_2) for altering pH. The remaining three channels provide the broth solution including solvent and nutrients. One of these latter streams can also be utilized to provide any additional requirements for the system such as antifoaming agents. Antifoaming agents are sometimes necessary to prevent production of foam and bubbles that can damage cells within the broth. The feed of the various streams into the chamber provides enough turbulence for mixing of the different streams. Flow within microfluidic devices is characterized by a low Reynolds number indicating the formation of lamina. While the turbulence created by the injection streams should provide sufficient mixing before the development of laminar flow, pilon-like obstructions 56 are placed in the flow path of the stream leaving the primary mixing chamber in order to enhance mixing of the lamina. By splitting a main stream into substreams followed by reunification, turbulence is introduced in the flow path, and a mechanism other than simple diffusion is used to facilitate further mixing. The length of this mixing field can be lengthened or shortened depending on the system requirements.

Referring now to Fig. 4, heating/dispersion unit 14 is shown. Unit 14 can be formed as described above with respect to other units of the invention. Unit 14 includes an inlet 60 in fluid communication with a plurality of outlets 62 in embodiments where dispersion as described below is desirable. In operation, a stream of homogeneous fluid exiting the mixing unit (feed broth in the specific microbioreactor embodiment shown) enters a dispersion matrix defined by a plurality of obstructions dividing the stream into separate flow paths directed toward the separate outlets 62. The dispersion matrix is sandwiched between two temperature control elements 20 and 24 which, as illustrated, include fluid flow channels 28 etched in a silicon article. Control unit 24 is positioned underneath unit 14, thus etched channel 28 is sealed by the bottom of unit 14. Control unit 20 is positioned atop unit 14 such that the bottom of unit 20 seals and defines the top of diffusion unit 14. A cover (not shown) can be placed a top unit 20 to seal channel 28.

Rather than for mixing, as in the previous case (Fig. 3), the splitting of the streams is to disperse the medium for its entrance into the reactive chamber in the next unit operation. In traditional reactor systems, fluid flow about a packing material containing catalysts produces the desired reaction. However, if the fluid is not evenly

dispersed entering the chamber, the fluid will flow through a low resistance path through the reactor and full, active surface area will not be utilized. Dispersion in this case is to optimize reactor efficiency in the next stage.

With regard to the heating function of this unit, the platform functions as a miniaturized, traditional heat exchanger. Etched silicon platforms both above and below the central platform serve to carry a heated fluid. Cells typically require their environment to have a temperature of ~30 °C. The fluids flowing in the etched coils both above and below the broth flow channel heating the broth through the thin silicon layer. The temperature of the fluid in the upper and lower heat exchangers can be modified to ensure proper temperature for the broth. Additionally, the platform can be extended for increased heating loads.

Although a combination heating/dispersion unit is shown, unit 14 can be either a dispersion unit or a heating unit. For example, dispersion can be provided as shown, without any temperature control. Alternatively, no dispersion need be provided (inlet 60 can communicate with a single outlet 62, which can be larger than the outlets as illustrated) and heating units can be provided. Cooling units can be provided as well, where cooling is desired. Units 20 and 24 can carry any temperature-control fluid, whether to heat or cool.

Referring now to Fig. 5, reaction chamber 16 is shown, including temperature control units 22 and 26, in expanded form. Units 22 and 26 can be the same as units 20 and 24 as shown in Fig. 4, with unit 22 defining the top of reaction chamber 16. Reaction unit 16 includes an inlet 70 fluidly communicating with an outlet 72 and a reaction chamber defined therebetween. The reaction chamber, in microreactor embodiments of the invention, has a volume of less than one milliliter, or other lower volumes as described above in connection with mixing unit 12. Inlet 70 is connectable to a source of a chemical or biological starting material, optionally supplied by mixing unit 12 and heating/dispersion unit 14, and outlet 70 is designed to release the product of a chemical or biological reaction occurring within the chamber involving the starting material. Unit 16 can be formed from materials as described above.

The reactor unit is the core of the process. While the unit is designed to be interchangeable for biological or pharmaceutical reactions, the specific application as shown is for cell cultivation. As in the case of the previous unit, temperature control units such as heat exchanger platforms will sandwich the central reaction chamber. The

heat exchangers will maintain the temperature of the reaction unit at the same temperature as discussed for the cell broth.

A feature of the unit is heterogeneous reaction on a supported matrix. Cell feed enters the reaction chamber under the proper pH, O_2 concentration, and temperature for cell cultivation. Cells, immobilized onto the silicon framework at locations 74 either by surface functionalization and subsequent reaction or entrapment within a host membrane, metabolize the nutrients provided by the feed stream and produce a product protein. The initial reaction platform can be a two-dimensional array of cells both on the top and bottom of the reaction chamber. This arrangement is to prevent a large pressure drop across the unit which would be detrimental to flow.

In this unit, oxygen and nutrients are diffused from the flowing stream to the immobilized cells. The cells, in turn metabolize the feed, and produce proteins which are swept away in the flowing stream. The flowing stream then enters the fourth chamber which removes the protein product from the solution.

Referring again to Fig. 1, it can be seen how dispersion unit 14 creates an evenly-divided flow of fluid (reactant fluid such as oxygen and nutrients in the case of cell cultivation) across each of locations 74 in reaction to chamber 16.

Referring now to Fig. 6, separation unit 18 is shown in greater detail, in expanded view. Separation unit 18 defines a central unit including an inlet 80 communicating with an outlet 82, and a fluid pathway 84 connecting the inlet with the outlet. Unit 18 can be fabricated as described above with respect to other components of the invention, and preferably is etched silicon. It may be desirable for fluid path 84 to completely span the thickness of unit 18 such that the pathway is exposed both above and below the unit. To maintain structural integrity, pathway 84 can be etched to some extent but not completely through unit 18 as illustrated, and a plurality of holes or channels can be formed through the bottom of the pathway exposing the bottom of the pathway to areas below the unit. Inlet 80 can be connectable to the outlet of reaction chamber 16, and outlet 82 to a container for recovery of carrier fluid.

In the embodiment illustrated, membranes 34 and 36 cover exposed portions of fluid pathway 84 facing upward or downward as illustrated. Membranes 30 and/or 36 can be any membranes suitable for separation, i.e. extraction of product through the membrane with passage of effluent, or carrier fluid, through outlet 82. Those of ordinary skill in the art will recognize a wide variety of suitable membranes including size-

selective membranes, ionic membranes, and the like. Upper and lower extraction solvent fluid units 30 and 32, which can comprise materials as described above including etched silicon, each include a fluid pathway 86 connecting an inlet 88 with an outlet 90. Fluid pathway 86 preferably is positioned in register with fluid pathway 84 of unit 18 when the separation unit is assembled. In this way, two flowing streams of solvent through channels 86 of units 30 and 32 flow counter to the direction of flow of fluid in channel 84 of unit 18, the fluids separated only by membranes 34 and 36. This establishes a counter-current tangential flow filtration membrane system. By concentration gradients, products are selectively extracted from channel 84 into solvent streams flowing within channels 86 of unit 30 or 32. Product is recovered through the outlet 90 of units 30 or 32 and recovered in a container (not shown) having a volume that can be greater than 1 liter. Outlets 90 thereby define carrier fluid outlets, and a fluid pathway connects inlet 80 of unit 18 with the carrier fluid outlets 90 of units 30 and 32, breached only by membranes 34 and 36. Carrier fluid outlet 82 can be made connectable to a recovery container for recycling of reaction carrier fluids. In the example of a microbioreactor, residual oxygen and nutrients are recovered from outlet 82 and recycled back into the feed for the process.

The flowing streams of extraction solvent in channels 86 can be set at any desired temperature using temperature control units (not illustrated). In the case of a microbioreactor, these fluids can be set at approximately 4°C. The low temperature is needed to maintain the efficacy of the protein products and prevent denaturation. Additionally, several purification and clarification steps are often performed in industrial application. The necessity of further purification is remedied by the use of additional units in series.

Embedded within the production process can be control systems and detectors for the manipulation of temperature, pH, nutrients, and oxygen concentration. Where a microbioreactor is used, the viability of cells is dependent upon strict limits for the parameters mentioned above. Narrow set-point ranges, dependent on the cell system selected, can be maintained using thermocouples, pH detectors, O_2 solubility detectors, and glucose detectors between each unit. These measurements will determine the heat exchanger requirements, O_2, CO_2, N_2, and nutrient inputs.

Diaphragm and peristaltic pumps can be used to provide the necessary driving force for fluid flow in the units. Such pumps are also used to maintain flow in the heat exchanger units.

It is a feature of the invention that many of the microreactors as illustrated can be arranged in parallel. Specifically, at least ten reactors can be constructed to operate in parallel, or in other cases at least about 100, 500, 1,000, or even 10,000 reactors can be constructed to operate in parallel. These reactors can be assembled and disassembled as desired.

It is another feature of the invention that individual units 12, 14, 16, and 18 can be constructed and arranged to be connectable to and separable from each other. That is, any arrangement of individual components can be created for a desired reaction. For example, with reference to Fig. 1, heating/dispersion unit 14 may not be necessary. That is, outlet 52 of mixing unit 12 can be connectable to either inlet 60 of heating/dispersion unit 14, or inlet 70 of reaction unit 16 where a heating/dispersion unit is not used. Moreover, assembly and disassembly of reactors to create a system including many, many reactors operating in parallel, as described above, or in series is possible because of the connectability and separability of the components from each other to form systems containing specific desired components, and any number of those or other systems operating together. Equipment for connection and separation of individual components of a reactor can be selected among those known in the art, as can systems for connection of a variety of reactors in parallel or in series. Systems should be selected such that the individual components can be connectable to and separable from each other readily by laboratory or production-facility technicians without irreversible destruction of components such as welding, sawing, or the like. Examples of known systems for making readily reversible connections between components of reactors or between reactors to form parallel reactors or series reactors include male/female interconnections, clips, cartridge housings where components comprise inserts within the housings, screws, or the like.

Those skilled in the art would readily appreciate that all parameters listed herein are meant to be exemplary and that actual parameters will depend upon the specific application for which the methods and apparatus of the present invention are used. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto,

the invention may be practiced otherwise than as specifically described. In the claims the words "including", "carrying", "having", and the like mean, as "comprising", including but not limited to.

What is claimed is:

CLAIMS

1. A chemical or biochemical reactor comprising:

a reaction unit including a chamber having a volume of less than 1 ml, an inlet to the chamber connectable to a source of a chemical or biological starting material, and an outlet of the chamber for release of a product of a chemical or biological reaction involving the starting material; and

a collection chamber connectable to the outlet of the reaction chamber, the collection chamber having a volume of greater than 1 liter.

2. A reactor as in claim 1, the reaction chamber having a volume of less than about 100 microliters.

3. A reactor as in claim 1, the reaction chamber having a volume of less than about 10 microliters.

4. A reactor as in claim 1, the reaction chamber having a volume of less than about 5 microliters.

5. A reactor as in claim 1, the reaction chamber having a volume of less than about 1 microliter.

6. A reactor as in any preceding claim, wherein the reaction unit comprises an etched portion of an article.

7. A reactor as in claim 6, wherein the reaction unit chamber comprises etched silicon.

8. A reactor as in any preceding claim, wherein the collection chamber comprises etched silicon.

9. A reactor as in any preceding claim, further comprising a mixing unit fluidly connectable to the inlet of the reaction chamber.

10. A reactor as in claim 9, the mixing unit including an outlet connectable to the inlet of the reaction chamber, a plurality of inlets each in fluid communication with the outlet and a mixing chamber between plurality of inlets and of the outlet.

11. A reactor as in claim 10, wherein the mixing unit chamber is free of active mixing elements.

12. A reactor as in claim 11, wherein the mixing chamber is constructed and arranged to coalesce a plurality of reactant fluids provided through the plurality of inlets and to cause turbulence in the fluids thereby mixing and delivering a mixture of the reactant fluids through the outlet of the mixing chamber.

13. A reactor as in claim 12, wherein the mixing unit includes a fluid flow path between the plurality of inlets and the outlet and a plurality of obstructions in the flow path constructed to cause mixture of fluid flowing through the flow path.

14. A reactor as in any of claims 9-13, wherein the mixing unit is attachable to and separable from the reaction unit.

15. A reactor as in any of claims 9-14, wherein the mixing chamber includes a volume, between the plurality of inlets and the outlet, of less than 1 liter.

16. A reactor as in any of claims 9-14, wherein the mixing chamber includes a volume, between the plurality of inlets and the outlet, of less than 10 microliter.

17. A reactor as in any of claims 1-8, further comprising a heating unit having an inlet, and an outlet connectable to the inlet of the reaction chamber, the heating unit separable from and attachable to the reaction chamber.

18. A reactor as in any of claims 1-8, further comprising a heating unit having an inlet, and an outlet fluidly connectable to the inlet of the reaction chamber, the heating unit separable from and attachable to the reaction chamber.

19. A reactor as in claim 18, wherein the heating unit includes an inlet, and a plurality of outlets fluidly connected to the inlet.

20. A reactor as in any of claims 1-8, further comprising a heating and dispersion unit having an inlet, and an outlet connectable to the inlet of the reaction chamber, the heating and dispersion unit separable from and attachable to the reaction chamber.

21. A reactor as in claim 20, wherein the heating and dispersion unit includes an inlet and a plurality of outlets connected to the inlet.

22. A reactor as in claim 21, further comprising a mixing unit having a plurality of inlets communicating with a mixing chamber, the mixing chamber communicating with an outlet, wherein the outlets of the heating and dispersion units are connectable to the inlet of the reactor, and the inlet of the heating and dispersion unit is connectable to the outlet of the mixing unit.

23. A reactor as in any of claims 18-22, wherein the dispersion unit is constructed and arranged to maintain fluid exiting the unit through the plurality of outlets at a temperature of approximately 30°C.

24. A reactor as in any preceding claim, wherein the reaction chamber is constructed and arranged for cell cultivation.

25. A reactor as in claim 24, wherein the reaction chamber has a surface adapted for immobilization of cells.

26. A reactor as in any preceding claim, further comprising a separation unit having an inlet and an outlet, the inlet connectable to the outlet of the reaction chamber.

27. A reactor as in claim 26, wherein the separation unit is connectable to and removable from the reaction chamber.

28. A reactor as in either of claims 26 or 27, wherein the separation unit includes an inlet connectable to the outlet of the reaction chamber, a carrier fluid outlet, a fluid pathway connecting the inlet with the carrier fluid outlet, and a size-selective membrane positioned to contact fluid flowing from the inlet to the fluid carrier outlet.

29. A reactor as in claim 28, wherein the membrane has a first side positioned to contact fluid flowing from the inlet to the fluid flow outlet and an opposing second side defining in part a product extraction solvent flow pathway.

30. A reactor as in either of claims 28 or 29, wherein the carrier fluid outlet is connectable to a recovery container for recycling of reaction carrier fluid.

31. A reactor as in any preceding claim, further comprising at least one sensor of temperature, pH, oxygen concentration, or pressure.

32. A reactor as in claim 31, comprising sensors of each of temperature, pH, and oxygen concentration.

33. A reactor as in any preceding claim, including a plurality of reaction chambers, attachable to and separable from each other, constructed and arranged to operate in parallel.

34. A reactor as in claim 33, comprising at least 10 reaction chambers constructed to operate in parallel.

35. A reactor as in claim 33, comprising at least 100 reaction chambers constructed to operate in parallel.

36. A reactor as in claim 33, comprising at least 500 reaction chambers constructed to operate in parallel.

37. A reactor as in claim 33, comprising at least 1,000 reaction chambers constructed to operate in parallel.

38. A reactor as in claim 33, comprising at least 10,000 reaction chambers constructed to operate in parallel.

39. A method comprising:

carrying out a chemical or biological reaction in a plurality of reaction chambers operable in parallel, each reaction chamber having a volume of less than 1 ml; and

discharging product of the reaction from the plurality of reaction chambers simultaneously into a collection chamber having a volume of greater than 1 liter.

40. A method as in claim 39, wherein the reaction is one of cell cultivation, catalysis, pharmaceutical production, hazardous chemical production, or chemical remediation of warfare reagents.

41. A method as in claim 40, wherein the reaction involves cell cultivation.

42. A method as in claim 41, involving passing a feedstream across immobilized cells and recovering a protein product in the collection chamber.

43. A method as in any of claims 39-42 comprising carrying out the chemical or biological reaction in parallel in at least 10 reaction chambers, and discharging product from each of the reaction chambers into the collection chamber.

44. A method as in any of claims 39-42 comprising carrying out the chemical or biological reaction in parallel in at least 100 reaction chambers, and discharging product from each of the reaction chambers into the collection chamber.

45. A method as in any of claims 39-42 comprising carrying out the chemical or biological reaction in parallel in at least 500 reaction chambers, and discharging product from each of the reaction chambers into the collection chamber.

46. A method as in any of claims 39-42 comprising carrying out the chemical or biological reaction in parallel in at least 1,000 reaction chambers, and discharging product from each of the reaction chambers into the collection chamber.

47. A chemical or biochemical reactor system comprising:

at least ten individuated chemical or biochemical reactors constructed and arranged for operation in parallel, and seperable to a non-parallel operative state and re-attachable to each other for operation in parallel , each including a reaction chamber having a volume of less than 10 ml.

48. A chemical or biochemical reactor system comprising:

a mixing chamber including a plurality of inlets connectable to a plurality of sources of chemical or biochemical reagents and an outlet;

a reaction chamber connectable to and removable from the mixing chamber, the reaction chamber having a volume of less than 1 ml, an inlet to the chamber connectable to and removable from the outlet of the mixing chamber, and an outlet of the chamber for release of a product of a chemical or biological reaction involving the starting material.

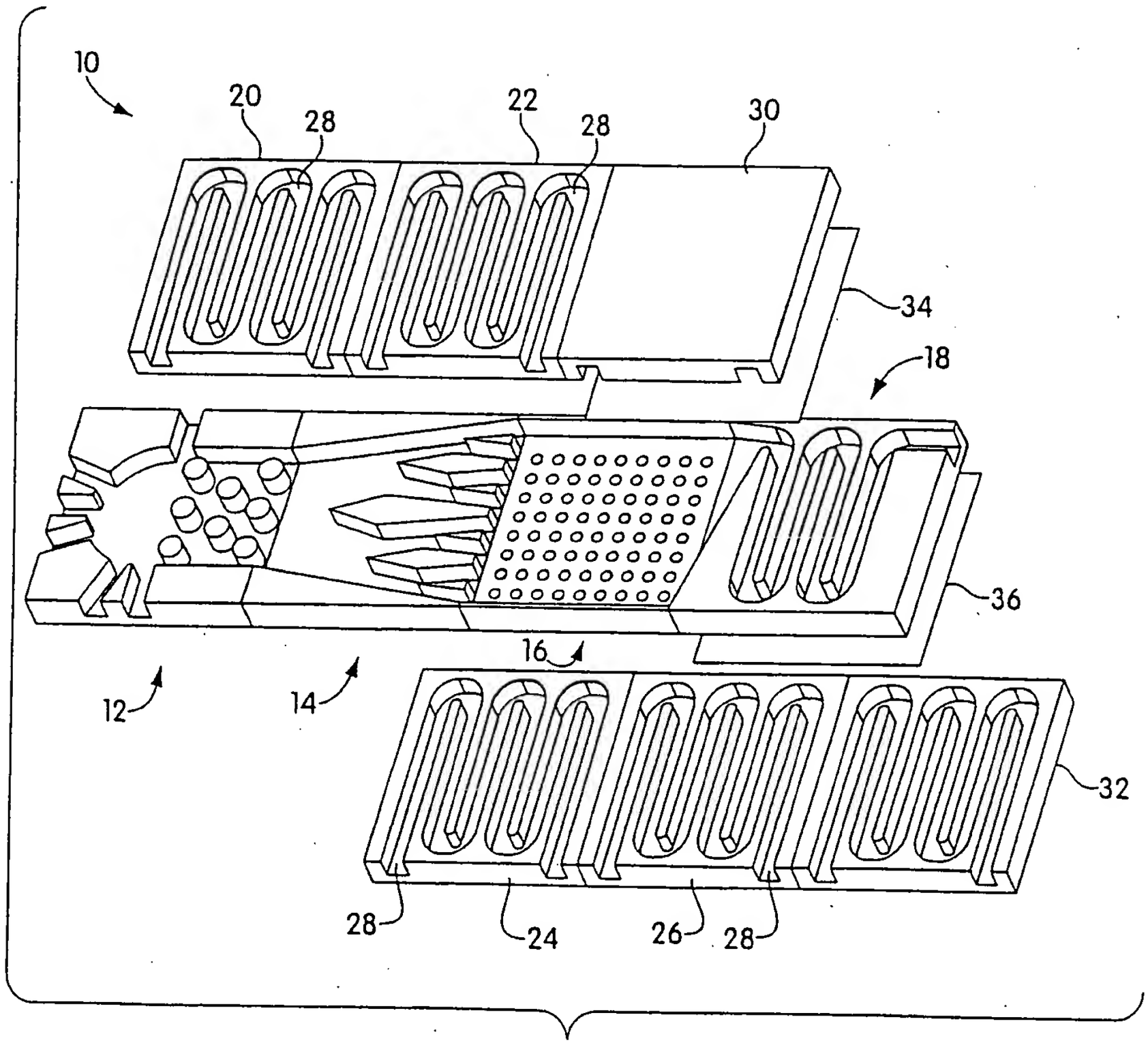

Fig. 1

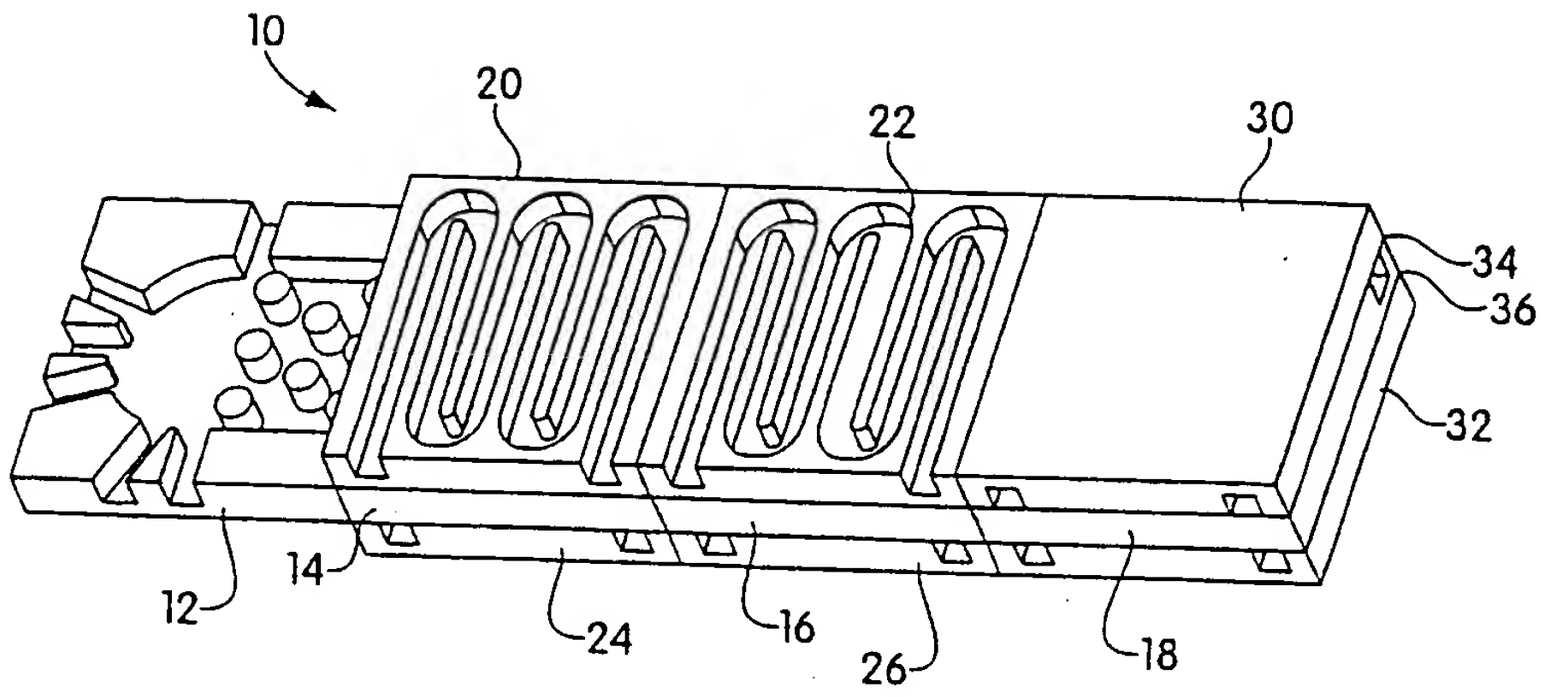

Fig. 2

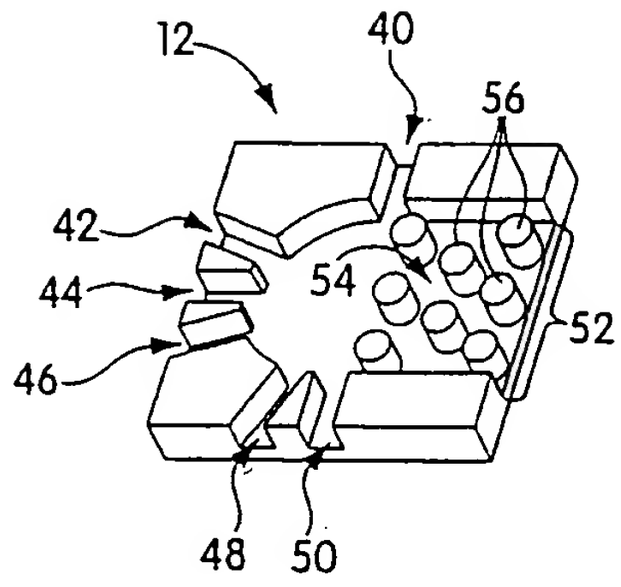

Fig. 3

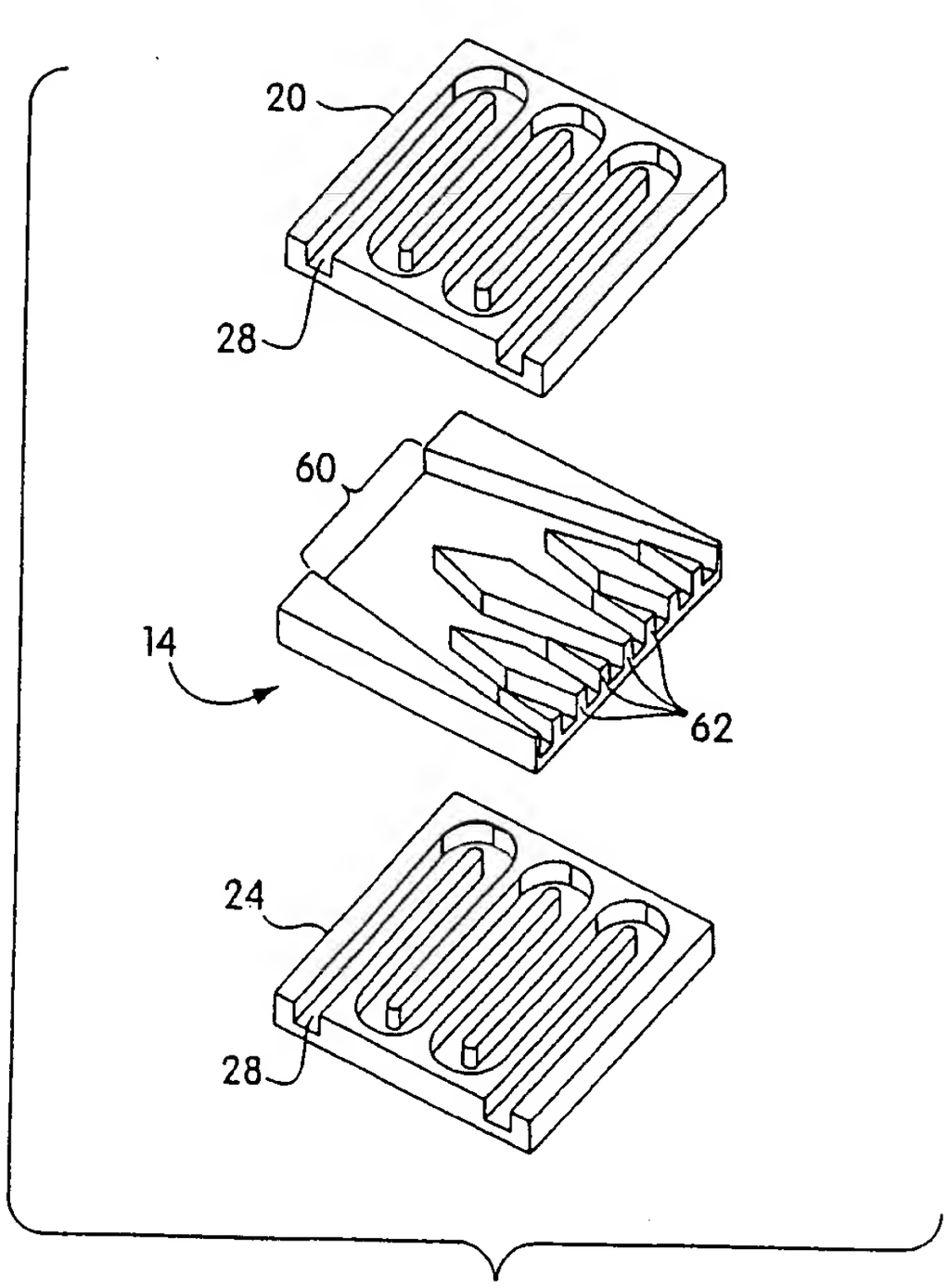

Fig. 4

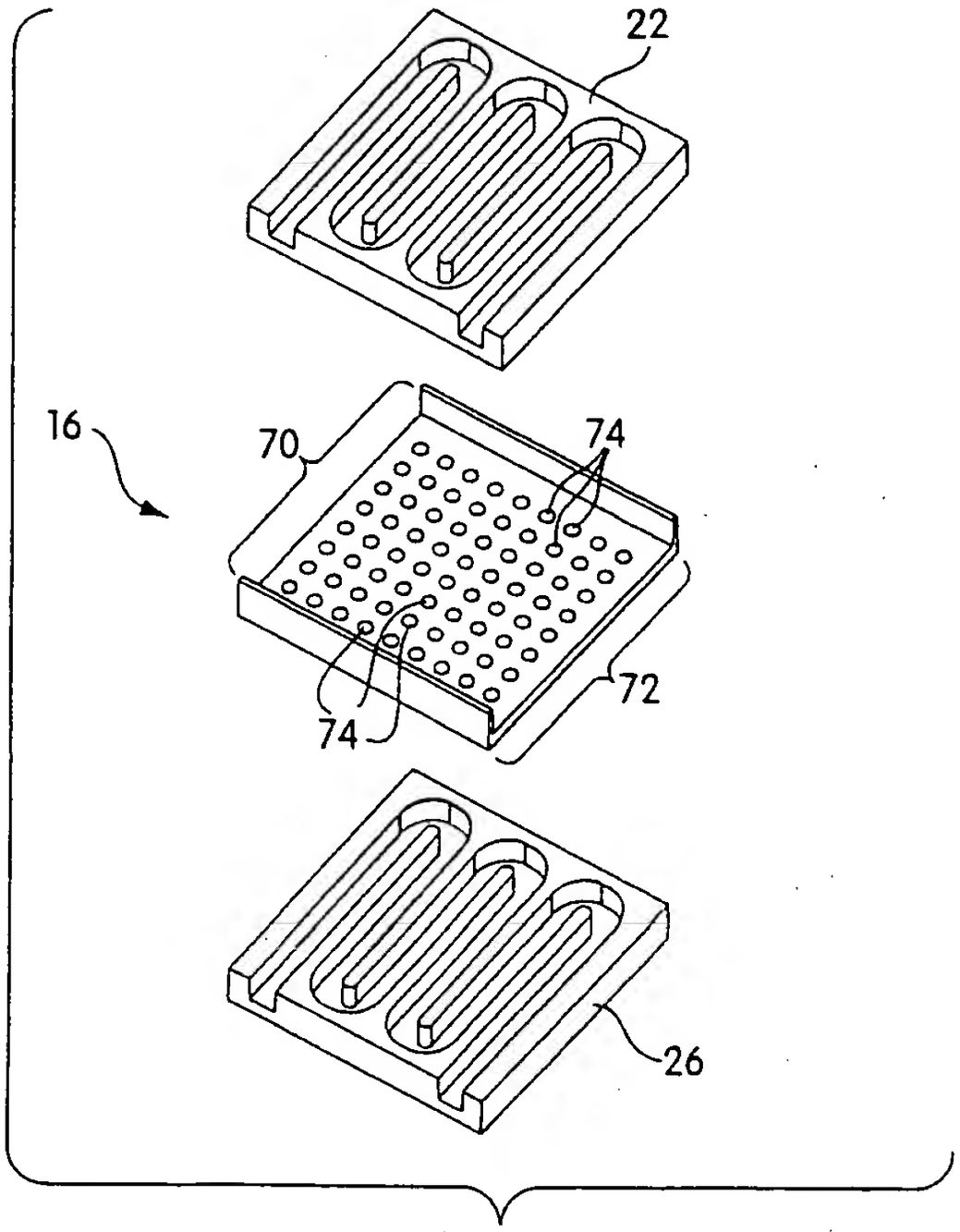

Fig. 5

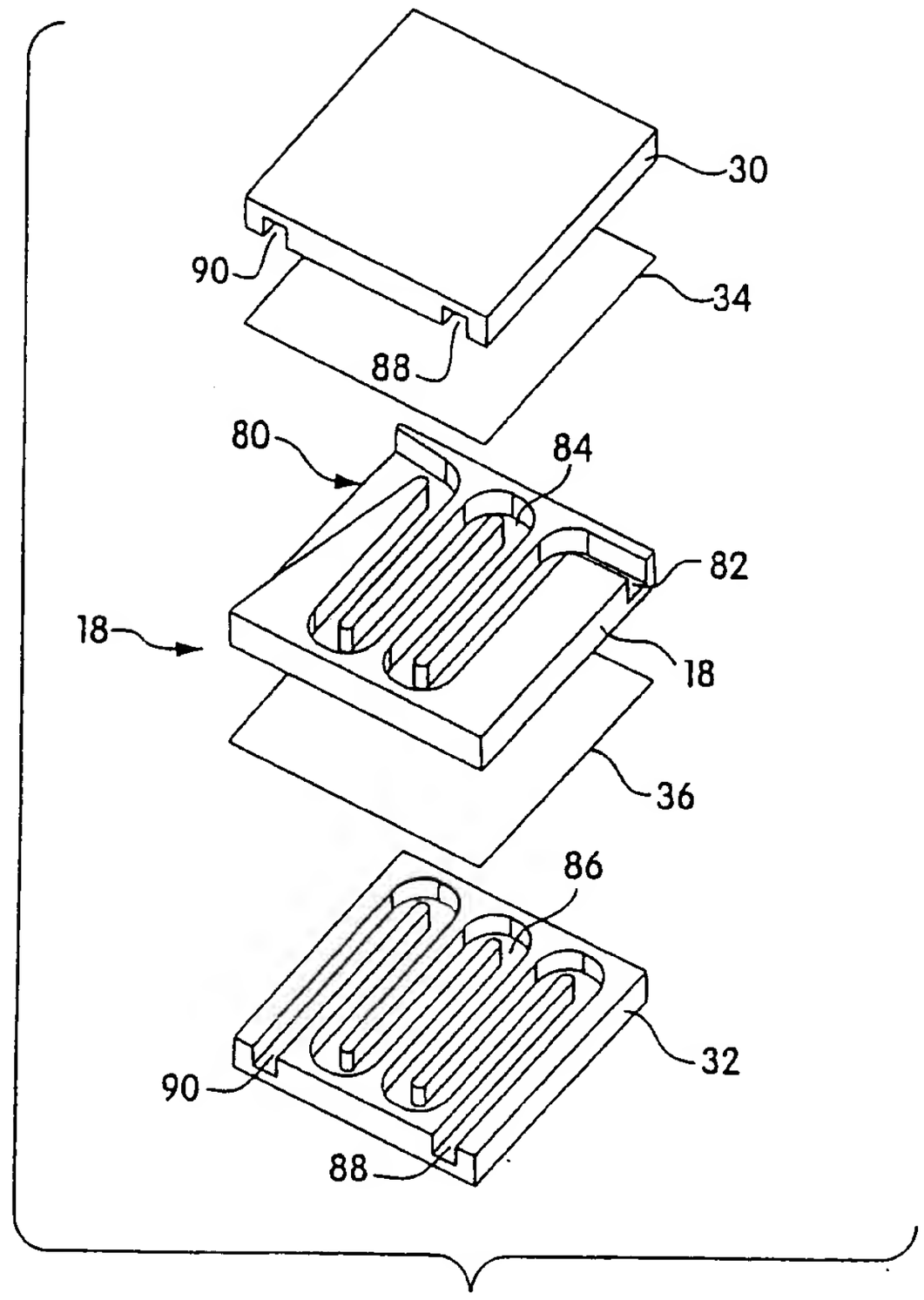

Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/07679

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :B01L 3/00; B01J 19/00, 8/00, 8/04

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 422/99, 130, 187, 189, 198, 236, 239, 145, 142, 188, 196, 240, 102

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

East and West; key terms: microreactor, mixing chamber, reaction chamber, collection chamber

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,639,423 A (NORTHRUP et al) 17 June 1997, abstract, column 4 line 49 - column 5 line 9; column 6 line 65-column 8 line 47.	1-10, 12, 14-18, 24-245, 31-32
Y	US 5,674,742 A (NORTHRUP et al) 07 October 1997, abstract,; column 1 lines 53-65; column 2 line 36 - column 3 line 4; Description of Preferred Embodiment	1-10, 12, 14-18, 24-25, 31-32
Y	US 5,646,039 A (NORTHRUP et al) 08 July 1997, abstract; column 1 lines 52-64, column 2 line 36 - column 3 line 4, Description of Preferred Embodiment	1-10, 12, 14-18, 24-25, 31-32
Y	US 5,856,174 A (LIPSHUTZ et al) 05 January 1999, Summary of Invention, column 16 lines 2 - 65	1-10, 24-26

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
26 APRIL 2001	08 JUN 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Carol Rudolph BRIAN GORDON Telephone No. (703) 308-0661

Form PCT/ISA/210 (second sheet) (July 1998) *

INTERNATIONAL SEARCH REPORT

Inter ›nal application No.
PCT/US01/07679

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	US 5,976,472 A (CHATTERJEE et al) 02 November 1999, column 4 lines 47-56, colmun 5 lines 43 - column 5 line 21, column 7 lines 14-40.	1-10, 12 ------ 17-18
A	US 5,436,129 A (STAPELTON) 25 July 1995, column 2 lines 24-34, column 11 lines 28-32,	1, 24, 25
A	US 5,840,258 A (HYPPANEN) 24 November 1998, abstract, column 1 lines 42-52, column 2 lines 52-64, column 5 line 66-column 6 line 50.	1-38
A	US 5,595,712 A (HARBSTER et al.) 21 January 1997, abstract, column 4 lines 54-63, column 5 lines 6-11 and 54-64	1-38
P, Y	US 6,043,080 A (LIPSHUTZ et al) 28 March 2000, see abstract, column 2, lines 14-65; column 4, lines 28-40; column 13 line 56-column 14 line 29, lines 53-57; column 15, lines 30-42, line 65-column 16 line 6, lines 41-54; olumn 18, lines 1-20; column 20 line 42-column 21, line 13	1-10, 24-26
P, Y	US 6,171,850 B1 (NAGLE et al.) 09 January 2001, entire document	11-10, 15-17

INTERNATIONAL SEARCH REPORT

Inter national application No.
PCT/US01/07679

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-38

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Intern nal application No.
PCT/US01/07679

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

422/99, 130, 187, 189, 198, 236, 239, 145, 142, 188, 196, 240, 102

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-38, drawn to a chemical or biochemical reactor.
Group II, claim(s) 39-46, drawn to a method of carrying out a chemical or biological reaction.
Group III, claim(s) 47, drawn to a chemical or biochemical reactor system.
Group IV, claim 48, drawn to a chemical or biochemical reactor system.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The method of Group II does not require the use of a reactor that comprises a chamber connectable to a source of a chemical or biological starting material, and an outlet of the chamber for release of a product of a chemical or biological reaction involving the starting material; and a collection chamber connectable to the outlet of the reaction chamber.

The apparatus of Groups I and IV do not comprise a plurality of reaction chambers operable in parallel as that of the method of Group II.

The apparatus of Group I, method of Group II, and system of IV do not comprise at least ten individuated chemical or biochemical reactors constructed and arranged for operation in parallel, and separable to a non-parallel operative state and re attachable to each other for operation in parallel.